

Title: NOVEL MEGAKARYOCYTIC PROTEIN TYROSINE KINASES

Inventor(s): Axel ULLRICH et al. Appl. No.: 08/426,509

CTCGCTCCAAGTTGTGCAGCCGGACCGCCTCGGGGTGTGCAGCCGGCTCGCGGAGGCCCTCCTGGGGGGGG	90	
GCGCCCCTGAGCAGAAAACAGGAAGAACCAGGCTCGGTCCAGTGGCACCCAGCTCCCTACCTCCTGTGCCAGCCGCCTGGCCTGTGGCA	180	•
GGCCATTCCCAGCGTCCCCGACTGTGACCACTTGCTCAGTGTGCCTCTCACCTGCCTCAGTTTCCCTCTGGGGGGGG	270	
Sma I		
GCTCTCTGGTTTCCTGGCGGCATTTCACGGCTGTGATTCTGCTGAGGAACTTCCCCGGGTGAGCCCCCGGTTCCTCCGAGCCTGCCACC G S L V S W R A F H G C D S A E E L P R V S P R F L R A W H	360	
Sma I		
CCCCTCCCGTCTCAGCCAGGATGCCAACGAGGCGCTGGGCCCCCGGCACCCCGGCAGCCAGTGTATCACCAAATGCGAGCACACCCGCCCCAAGCCAG PPPVSARMPTRRWLAPGTQCITKCEHTRPKP	450	
Ştu! Kpnī		
GGGAGCTGGCCTTCCGCAAGGGCGACGTGGTCACCATCCTGGAGGCCTGCGAGAACAAGAGCTGGTACCGCGTCAAGCACCACACCAGTG G E L A F R K G D V V T I L E A C E N K S W Ý R V K H H T S	540 SI	Н 3
Pvull		
GACAGGAGGGGCTGCTGGGGGGGGGGGGGGGGGGGGGGG	630	
PvullPstl		
GGAAGATCTCGGGCCAGGAGGCTGTCCAGCAGCTGCAGCCTCCCGAGGATGGGCTGTTCCTGGTGCGGGAGTCCGCGCGCCCACCCCGGCG	720	
GKISGQEAVQQLQPPEDGLFLVRESARHPG	Sł	H 2
Clal		
ACTACGTCCTGTGCGTGAGCTTTGGCCGCGACGTCATCCACTACCGCGTGCTGCACCGCGACGGCCACCTCACAATCGATGAGGCCGTGT D Y V L C V S F G R D V I H Y R V L H R D G H L T I D E A V	810	
	900	
F F C N L M D M V E H Y S K D K G A I C T K L V R P K R K H		

, Similar

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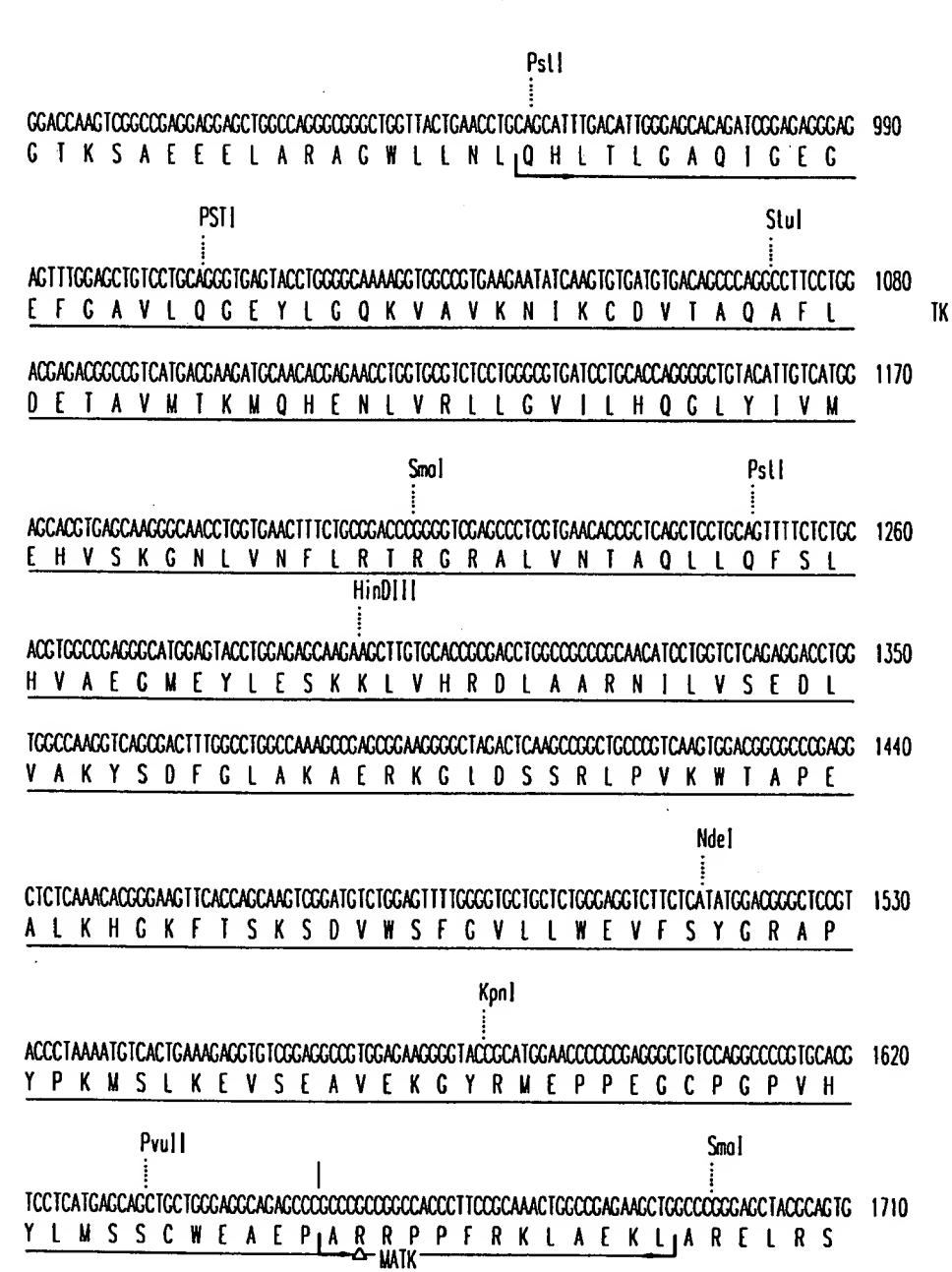


FIG.1B

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CACGIGCCCCAGCCTCCGTCTCAGGCCAGGACGCCGACGCCTCCACCTCGCCCCCGAAGCCAGGACCCCTGACCCCACCCGGTGGGGCCCT

A G A P A S V S G Q D A D G S I S P R S Q E P

TGGCCCCAGAGGACGGAGGAGTGGAGAGTGCGGCGTGGGGGCCCCTGACCAGGCCCCAAGGAGGGGGCGCAAGTCATCCTCCTGG

1890

ATICTAAGGACTCTAAAAAA 2000

FIG.1C

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CCC	CTI	Ш	[GC]	TAC	GAGC	110	GAGA	GTC	AAA.	G	AG	GAC	CCA	CAT	GTA	TAC	HTC	CCC	CICI	AGC	GAG	Ϊ,	_AG	GAT	GAT	AAT M	ATG D	_	TACA	90	
AA/ K	TCT S	ATI I	CT/ L	AGA/ E	KGAA E	CTI L	CTI	CTC		vaga R							ATG M				AAT N		AAA K	CAA E		CII		• • •	TIG L	180	
ACC	XAA K	VACA	VAA(CII	TCC S)ATC Y	TAT Y	GAA E	TAT Y										VGGA G	TCC S	ATT	GAA E	ATT L	AAG K	AAA K	ATC 1	AGA R	IGI C	GTG V	270	
GAG E	K	GT/ V	IAAI N	ICT(GAG E	GAC E	CAG Q	ACC	CCT P	GTA V	GAG E	AGA R	CAG Q	TAC	CCA P	III F	CAC	ATI	GTC	TAT	AAA K	GAT D	CCC	CTI L	CIC	TAT: Y	GTC V	IAI: Y	IGCA A	360	PH
TCA S	_	_	_	_	CCGA R	_				_	GCA A		_			ATA 1	VACO R	CG1		CCC P		CIG	CTG	GTC V	AAC K	TAC Y	CAT H	AG1	_G	450	
TTC F	TTC F	GTG V	GAC D	0000 C	SAAG K	TTC F	CIG	TGT C	TGC C		CAG Q		_		_	-	· _		NTGT C	ACC T	CIC	TGG W	GAA E	GCA A	TAT Y	GCT A	AAT N	CTC	CAT H	540	
ACT	GCA A	GTC V	AA1 N	GAA E	GAG E		CAC H				ACC T	TTC F	CCA P	GAC D									•			CIC L			CAT D	630	
GCA A	CCA P			WCT S	•										AAG	I AAA	AAC	TAT		TCC	CAG	CCA		ICT					ICTA L	720	SH3
GCG A	CAA Q	TAT Y	GAC D	AGC S	AAC N			1		TAT		TCC	CAG	CCA	AAC	TTC	AAC	ATG		TAT	ATT				GAC D	TTC F	_	GAC D	CTGG W	810	
TGC W	٠.	GTA V																	CAA Q		-			GTG V	AAT N	CAC H	ACC T	ACC T	CTCA S	900	
AAG K	ATT 1	TCA S	TGG W																GAT D					GCT A	CGT G	AAC N	ATC 1	TCC	CAGA R	990	
TCA S	CAA Q	TCT S	GAA E	CAG Q	TTA L	CTC	AGA R	CAA Q	AAG K	GGA G	AAA K	GAA E	GGA G	GCA A	TTT.	ATG M	GTT V	AGA R	AAT N		AGC S	I CAA Q	GTG V	GGA G	ATG M	TAC.	ACA T	GTG V	STCC S	1080	SH4
	_																									TAC Y			GAA E	1170	

FIG.2A

AACTACTGTTTTGATTCCATTCCAAAGCTTATTCATTATCATCAACACAATTCAGCAGGCATGATCACACGGCTCCGCCACCCTGTGTCA	1260	
NYCFDSIPKLIH YHQHNSAGMITRLRHPVS	1200	
ACAAAGGCCAACAAGGTCCCCGACTCTGTGTCCCTCGGAAATGGAATCTGGGAACTGAAAAGAGAGAG	1350	
GGAAGTGGCCAGTTTGGAGTGGTCCAGCTGGCCAAGTGGAAGGGGCAGTATGATGTTGCTGTTAAGATGATCAAGGAGGGCTCCATGTCA G S G Q F G V V Q L G K W K G Q Y D V A V K M I K E G S M S	1440	
GAAGATGAATTCTTTCAGGAGCCCCAGACTATGATGAAACTCAGCCATCCCAAGCTGGTTAAATTCTATGCAGTGTGTTCAAAGGAATAC EDEFFQEAQTMIKKLSHPKLVKFYGVCSKEY	1530	
CCCATATACATAGTGACTGAATATATAAGCAATGGCTGCTTGCT	1620	ĬK
TTAGAAATGTGCTACGATGTCTGTGAAGGCATGGCCTTCTTGGAGAGTCACCAATTCATACACCGGGACTTGGCTGGTGAACTGCTTG	1710	
GTGGACAGAGATCTCTGTGGAAAGTATCTGACTTTGGAATGACAAGGTATGTTCTTGATGACCAGTATGTCAGTCA	1800	
ITTCCAGTCAAGTGGTCAGCCTCCAGAGGTGTTTCATTACTTCAAATACAGCAGCAAGTCAGACGTATGGGCATTTGGGATCCTGATGTGG	1890 -	
GAGGIGTICAGCCTGGGGAAGCAGCCCTATGACTIGTATGACAACTCCCAGGTGGTTCTGAAGGTCTCCCAGGGCCACAGGCTTTACCGG EVFSLGKQPYDLYDNSQVVLKVSQGHRLYR	1980	
CCCCACCTGGCATCGGACACCATCTACCAGATCATGTACAGCTGCTGGCACGAGCTTCCAGAAAAGCGTCCCACATTTCAGCAACTCCTG PHLASDTIYQIMYSCWHELPEKRPTFQQLL	2070	
TCTTCCATTGAACCACTTCGCGAAAAAGACAAGCATTGAAGAAGAAATTAGGAGTGCTGATAAGAATGAAT	2160	
TICATICATITIAAGGAAAGTAGCAAGGCATAATGTAATTTAGCTAGTTTTTAATAGTGTTCTCTGTATTGTCTATTATTTAGAAATGAA	2250	
CAAGGCAGGAAACAAAAGATTCCCTTGAAATTTAGGTCAAATTAGTAATTTTGTTTATGCTGCCCCTGATATAACACTTTCCAGCCTATA	2340	
GCAGAAGCACATTTCAGACTGCAATATAGAGACTGTGTTCATGTGTAAAGACTGAGCAGAACTGAAAAATTACTTATTCGATATTCATT	2430	
CTTTTCTTTATATTGTCATTGTCACAACAATTAAATATACTACCAAGTACAAAAAAAA		

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CCCGACTGGTCGAAAGACAGGACAGACTTGAAACAGCGGGAGAGCTCCTGGCGAAACGAAGACGTCGAGGTTTTACCAGGGATAAGAAG	90	
AAAAGACACCTTCCTAGTGAGCAGCTGCCCAGCTCCTGCTCAGTTTTGCCTCGGGGTAGCACCTCCAGCCACAGAAAGCAAGC	180	
TCTCTCCAGGTAGGACTTGCTGCAACCCAGCTGCTGGACTGATCTGAAACGGGACTTTGCATACTCTCCGAAGTATGGTGAGTTGGTGCT M V S W C	270	
GACTTCAAAGTTGCCTGGTGAAGGAAGATAAGGTGGATCGCAGAGACTAAGGGGAGAGGGGAGAGCCCTGCTCCTCTTCTCCCCACCAAG	360	
GCACAATGAGCAACATCTGTCAGAGCCTCTGGGAGTACCTAGAACCCTATCTCCCCTGTTTGTCCACGGAGGCAGACAAGTCAACCGTGA M S N I C Q R L W E Y L E P Y L P C L S T E A D K S T V	450	
TIGAAAATCCAGGGGGGGCTTIGCTCTCCCCAGTCACAGAGGCATGGCCACTACTTIGTGGCTTTIGTTTGATTACCAGGCTCGGACTGCTG 1 E N P G A L C S P Q S Q R H G H Y F V A L F D Y Q A R T A	540	
AGGACTIGAGCTICCGAGCAGGTGACAAACTICAAGTTCTGGACACTTTGCATGAGGGCTGGTGGTTTGCCAGACACTTGGAGAAAAGAC EDLSFRAGDKLQVLDTLHEGWWFARHLEKR	630	SH 3
GAGATGGCTCCAGTCAGCAACTACAAGGCTATATTCCTTCTAACTACGTGGCTGAGGAGCAGAAGCCTACAGGCAGAGCCGTGGTTCTTTG R D G S S Q Q L Q G Y I P S N Y V A E D R S L Q A E P W F F	720	4
GAGCAATCGGAAGATCAGATGCAGAGAACAACTATTATATTCAGAAAACAAGACCGGTTCCTTTCTAATCAGAGAAAGTGAAAGCCAAA G A I G R S D A E K Q L L Y S E N K T G S F L I R E S E S Q	810	SH 2
AAGGAGAATICICICITICAGTITTAGATGGAGCAGTIGTAAAACACTACAGAATTAAAAGACTGGATGAAGGGGGATTTTTTCTCACGC K G E F S L S V L D G A V V K H Y R I K R L D E G G F F L T	900	
GAAGAAGAATCTTTTCAACACTGAACGAATTTGTGAGCCACTACACCAAGACAAGTGACGGCCTGTGTGTCAAGCTGGGGAAACCATGCT RRRIFSTLNEFVSHYTK, TSDGLCVKLGKPC	990	
TANAGATCCAGGTCCCAGCTCCATTTGATTTGTCGTATAAAACCGTGGACCAATGGGAGATAGACCGCAACTCCATACAGCTTCTGAAGC LKIQVPAPFDLSYKTVDQWEIDRNSIQLLK	1080	
CATTGGGATCTGGTCAGTTTGGCGAAGTATGGGAAGGTCTGTGGAACAATACCACTCCAGTAGCAGTGAAAACATTAAAACCAGGTTCAA R L G S G Q F G E V W E G L W N N T T P V A V K T L K P G S	1170	
GGATCCAAATGACTTCCTGAGGGAGGCACAGATAATGAAGAACCTAAGACATCCAAAGCTTATCCAGCTTTATGCTGTTTGCACTTTAG B D P N D F L R E A Q I M K N L R H P K L I O L Y A V C T I	1260	

FIG.3A

Title: NOVEL
MEGAKARYOCYTIC PROTF TYROSINE KINASES Inventor(s): Axel ULLRICH et al. Appl. No.: 08/426,509

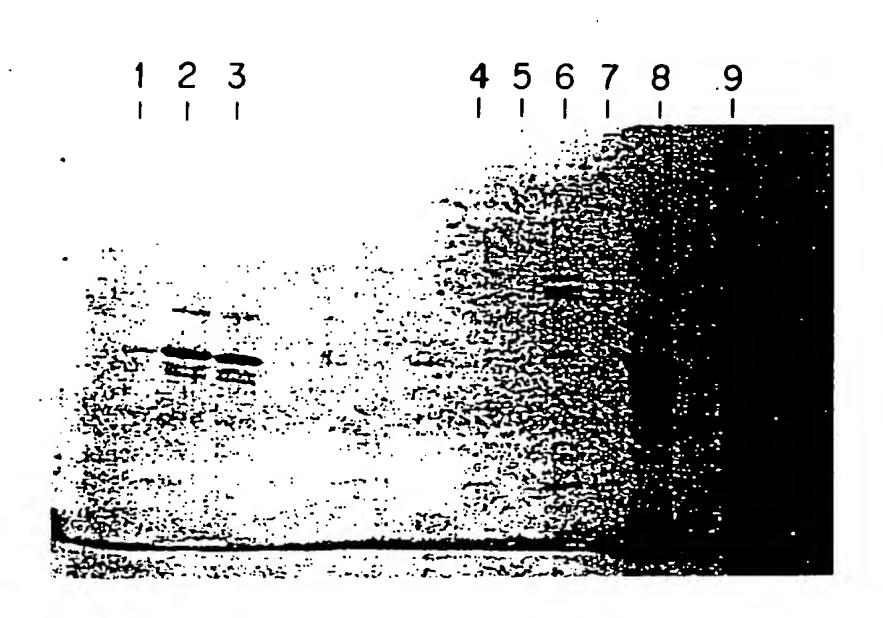
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		MKK1	MKK2
HUMAN	,		•
MEG/ERYTH	MEG-01 K562 MO7E HEL	+++ ++ ++ +++	+++ + + ++
MYELO/MAC	KG-1 HL-60 TF-1	+ + +	++ + +
B-CELL	ALL-1 RAJI DAUDI	_ _ _	+ - -
T-CELL	MOLT-3 JURKAT		
EPİTHELIAL	HELA		-
RODENT			
	BM SPLEEN THYMUS LIVER BRAIN	+ +++ - - +	+++ + - -
RAT NEURAL	P19	+	_

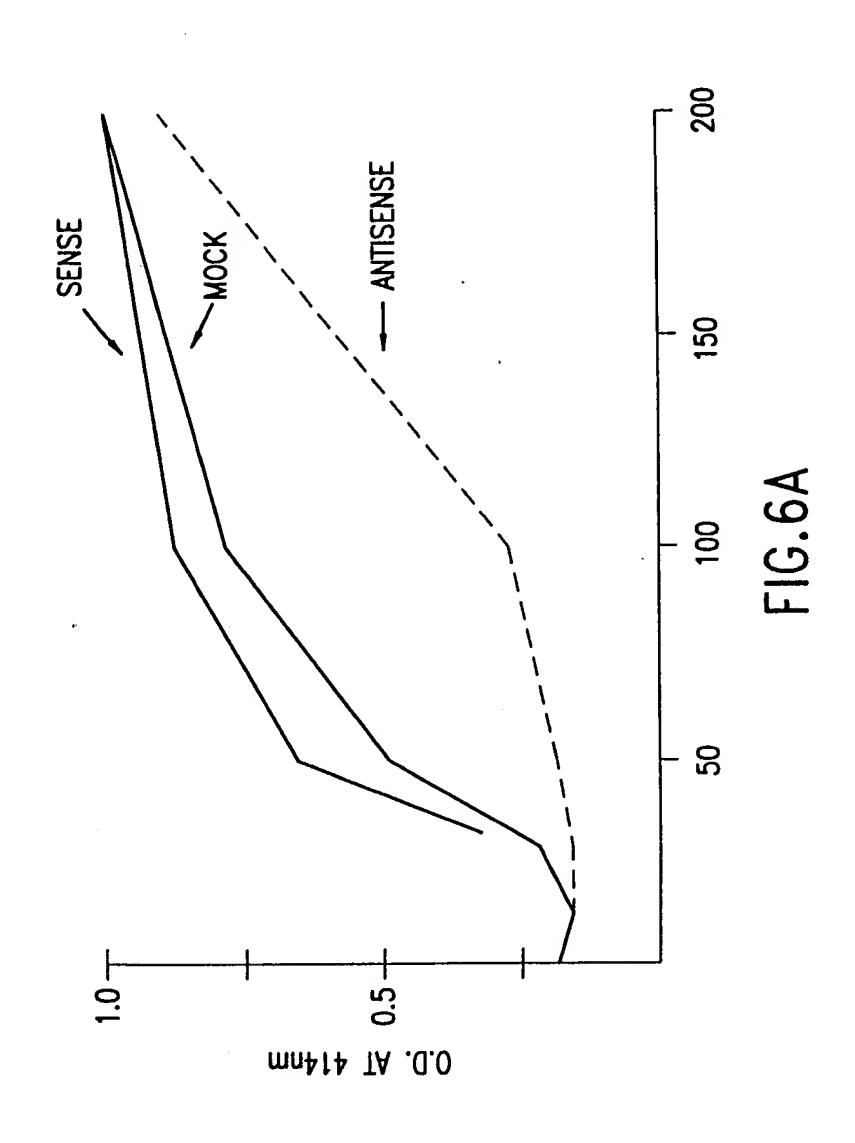
FIG.4

Title: NOVEL
MEGAKARYOCYTIC PROTEIN
TYROSINE KINASES

Inventor(s): Axel ULLRICH et al. Appl. No.: 08/426,509



F I G. 5



Title: NOVEL MEGAKARYOCYTIC PROTEIN TYROSINE KINASES. Inventor(s): Axel ULLRICH et al.

Appl. No.: 08/426,509

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MKKI PROTEIN EXPRESSION

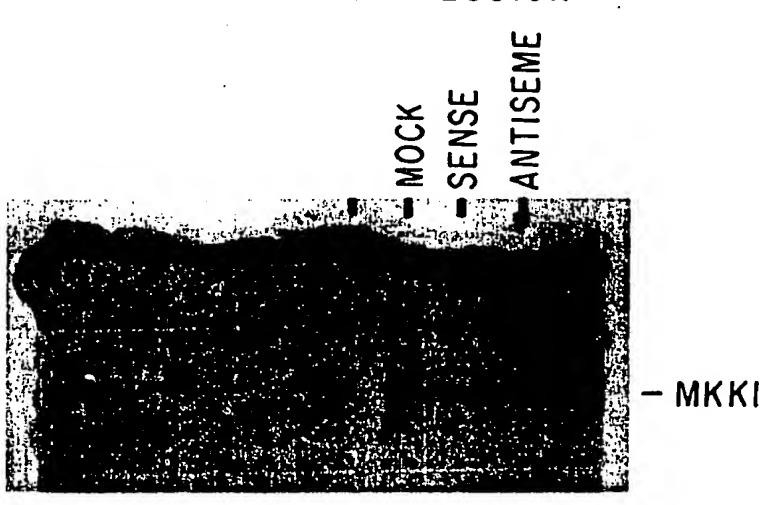


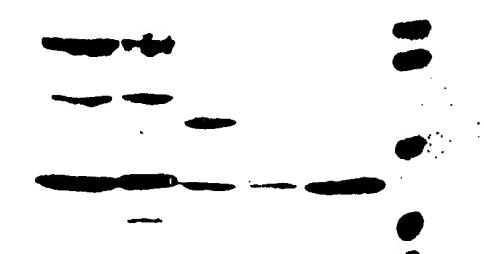
FIG. 6B

Title: NOVEL

MEGAKARYOCYTIC PROTEIN TYROSINE KINAŞES

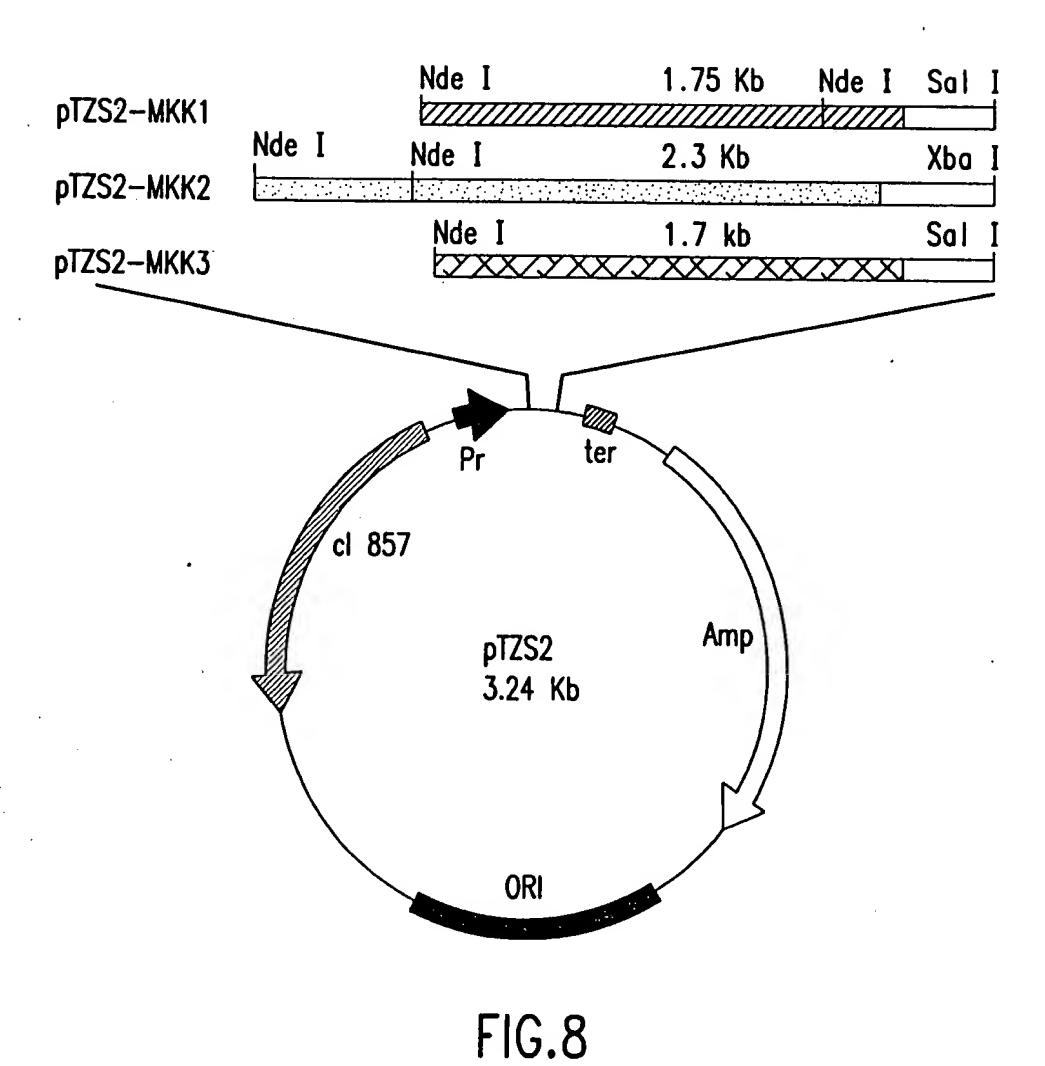
Inventor(s): Axel ULLRICH et al. Appl. No.: 08/426,509

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1 2 3 4 5 6

F1G. 7



1	MAGRGSLVSWRAFHGCDSAEELPRVSPRFL MSAIQAA	MKK1 aa hCSK (JH0559)
31 8	RAWHPPPVSARMPTRRWAPGTOCITKCEHT	MKK1 aa hCSK (JH0559)
61	R P K P G E L A F R K G D V V T I L E A C E N K S W Y R V K	MKK1 aa
22	G T A E Q D L P F C K G D V L T I V A V T K D P N W Y K A K	hCSK (JH0559)
91	HHTSGQEGLLAAGALREREALSADPKLSLM	MKK1 aa
52	NKV-GREGIIPANYVQKREGVKAGTKLSLM	hCSK (JH0559)
121	PWFHGKISGQEAVQQLQPPEDGLFLVRESA	MKK1 aa
81	PWFHGKITREQAERLLYPPETGLFLVREST	hCSK (JH0559)
151	R H P G D Y V L C V S F G R D V I H Y R V L H R D G H L T I	MKK1 aa
111	N Y P G D Y T L C V S C D G K V E H Y R I M Y H A S K L S I	hCSK (JH0559)
181 141	D E A V F F C N L M D M V E H Y S K D K G A I C T K L V R P D E E V Y F E N L M Q L V E H Y T S D A D G L C T R L I K P	MKK1 aa hCSK (JH0559)
211 171	K R K H G T K S A E E E L A R A G W L L N L Q H L T L G A Q K V M E G T V A A Q D E F Y R S G W A L N M K E L K L L Q T	MKK1 aa hCSK (JH0559)
241 201	I G E G E F G A V L Q G E Y L G Q K V A V K N I K C D V T A I G K G E F G D V M L G D Y R G N K V A V K C I K N D A T A	MKK1 aa hCSK (JH0559)
271	QAFLDETAVMTKMQHENLVRLLGVILHQ	MKK1 aa
231	QAFLAEASVMTQLRHSNLVQLLGVIVEEKG	hCSK (JH0559)
299	G L Y I V M E H V S K G N L V N F L R T R G R A L V N T A Q	MKK1 aa
261	G L Y I V T E Y M A K G S L V D Y L R S R G R S V L G G D C	hCSK (JH0559)
329	L L Q F S L H V A E G M E Y L E S K K L V H R D L A A R N I	MKK1 aa
291	L L K F S L D V C E A M E Y L E G N N F V H R D L A A R N V	hCSK (JH0559)
359 321	L V S E D L V A K V S D F G L A K A E R K G L D S S R L P V L V S E D N V A K V S D F G L T K E A S S T Q D T G K L P V	MKK1 aa hCSK (JH0559)

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K W T A P E A L K H G K F T S K S D V W S F G V L L W E V F K W T A P E A L R E K K F S T K S D V W S F G I L L W E I Y MKK1 aa hCSK (JH0559) SYGRAPYPKMSLKEVSEAVEKGYRMEPPEG 419 MKK1 oo SFG RVP Y PR I PL KD V V P R V E K G Y K M D A P D G 381 hCSK (JH0559) C P G P V H V L M S S C W E A E P A R R P P F R K L A E K L 449 MKK1 oo C PP AVY E VMK NC WH L D AAMR PSFL QLREQL hCSK (JH0559) 479 ARELRSAGAPASVSGQDADGSTSPRSQEP MKK1 aa hCSK (JH0559)

FIG.9B

1 1 1	IMIA A - VII L	ESIFIKRS	O Q K K KMS P N N Y K E R O Q K K K T S P L N F K K R O Q K R R T S P S N F K V R I	hAtk (158957)
31 30 31 4	IFILIL TIV H K	LSYYELYDE	DKMKRGSRKGSIEII ERGRRGSKKGSIDVI -HGKKRTLKGSIEL	- HALL (Y58057)
59 60 59 4	K I R C V E K K I T C V E T R I K C V E I	V N L E E Q T F V V P E K N P F V K S D	PERQIPRRGEESSE	- MKK2 oo M hAlk (X58957) - hTKT (L10717) - mTec (X5663)
78 90 70 4	[[S]PC	HYKLA bed	VYK DG L L Y VYAS NE E VY DEGPL Y V FSPTE E VHDN YL L Y V F A PD RE N F H S S P (hTKT (L10717)
98 120 98 17	SRSOWLK LRKRWIH SRORWVL SRDRWVK	ALOKEIRG OLKNVIRY ALKEETRN KLKEETKN	NPHLLVKYHSGFFVC NSDLVQKYHPCFWIC NNSLVPKYHPNFWMC NNNIMIKYHPKFWAC	MKK2 oo hAlk (X58957) hTKT (L10717) mTec (X5663)
128 150 128 47	G KFL C CQ GQY L C C S G KW R C C S GSYQC CR	QSCKAAPG QTAKNAMG QLEKLATG QTEKLAPG	CILWEAYANLHTAVN CQILENRNGSLKPGS CAQYDF CEKYNLFESSI	MKK2 aa hAlk (X58957) hTKT (L10717) mTec (X5663)
158 180 149 73	E E K H R V P [S H R K T K K T K N A S K K R K	IFPDRVLK PLPP PLPP	IPRAVPVLKMDAPSSTPEEDOILKKPLPPETPEDNR	MKK2 aa hAlk (X58957) hTKT (L10717) mTec (X5663)
188 206 166 89	STTLAQY PAAAPVSRPLW PPIPPEE	DNESKKNY TSELKK EPEETV ENTEEI	G S Q P P S S S T S L A Q Y D	MKK2 aa hAlk (X58957) hTKT (L10717) mTEC (X5663)

FIG. 10A

Title: NOVEL MEGAKARYOCYTIC PROTEIN —

TYROSINE KINASES Inventor(s): Axel ULLRICH et al. Appl. No.: 08/426,509

218 SNSKKI 225 YMPMNAI 182 YOTNDP 108 FOATEAI	C S Q P N F N M Q Y I P R E D F P N D L Q L R K G D E Y F I L E E S N E E L L D S S E L D L R L E R G Q E Y I I L E K N D	- DWWQV LPWWRA IHWWRV L·HWWRA	MKK2 aa hAlk (X58957) hTKT (L10717) mTec (X5663)
247 RKLKSS 255 RDKN 212 QDRN 138 RDK-	SSSEDVASSNOKERNVNH GQEGYIPSNYVTE-A GHEGYVPSSYLVEKS	T T S K I S	MKK2 oo hAtk (X58957) hTKT (L10717) mTec (X5663)
273	SSSEEENLDDYDWFAGN EDSIEMYEWYSKH PNNLETYEWYNKS YGWYCRN	MTRSQA ISRDKA	MKK2 oa hAlk (X58957) hTKT (L10717) mTec (X5663)
292 FOII K O	KGKEGAFMVRNSSQVGMY EGKEGGFIVRDSSKAGKY IGKEGAFMVRDSRTAGTY EDKEGGFMVRDSSQPGLY	TVSVFIA	MKK2 oo hAtk (X58957) hTKT (L10717) mTec (X5663)
322 KST-GD 280 KAVVSE	KKGTVKHYHVHTNAEN PQGVIRHYVVCSTPQS NNPCIKHYHIKETNDNPK GSSGFRHYHIKETATSPK	QYYLAE RYYVVAE	MKK2 oo hAtk (X58957) hTKT (L10717) mTec (X5663)
349 KHLFST 310 KYVFDS	I PKL I HY H Q H N S A G M I T R I P E L I N Y H Q H N S A G L I S R I P L L I N Y H Q H N G G G L V T R I P E I I E Y H K H N A A G L V T R	L R Y P V C	MKK3 aa hAtk (X58957) hTKT (L10717) mTec (X5663)
379 QQNKNA1 340 <u>FG</u> RQKA1	PDSVSLGNGIWELKREEIPSTAGLGYGSWEIDPKDLPVTAGLRYGKWVIDPSELPTIAGFSYDKWEINPSEL	TFLKEL	MKK2 oo hAtk (X58957) hTKT (L10717) mTec (X5663)
424 G S G Q F G 409 G T G Q F G 370 G S G Q F G [273 G S G L F G	VVQLGKWKGQYDVAVKMI VVKYGKWRGQYDVAIKMI JVHLGYWLNKDKVAIKTI VVRLGKWRAQYKVAIKAI	KEGSMS KEGSMS REGAMS REGAMC	MKK2 aa hAtk (X58957) hTKT (L10717) mTec (X5663)

Title: NOVEL MEGAKARYOCYTIC PROTEIN ~ TYROSINE KINASES

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454 E DEFF QE AQ TMMKLSHPKLVKFYG V.CSKEY
                                                   MKK2 aa
 439 E DEFTEEAKVMMNLSHEKLVQLYGVCTKQR
                                                   ThAlk (X58957)
 400 EEDFIEEAEVMMKLSHPKLVQLYGVCLEQA
                                                   hTKT (L10717)
    EEDFIEEAKVMMKLTHPKLVQLYGVCTQQK
                                                   mTec (X5663)
 484 PIYIVTEYISNGCLLNYLRSHGKGLEPSQL
                                                   MKK2 aa
 469 PIFILITEYMANGCLLNYLREMRHRFQTQQL
                                                   hAlk (X58957)
 430 PICLVFEFMEHGCLSDYLRIORGLIFIAAETL
                                                   hTKT (L10717)
       YIVTEFMERGCLLNFLRQRQGHFSRDML
                                                   mTec (X5663)
514 LEMCYDVCEGMAFLESHQFIHRDLAARNCL
                                                   MKK2 aa
499 LEMCKDVCEAMEYLESKOFLHRDLAARNCL
                                                   hAlk (X58957)
460 LGMCLDVCEGMAYLEEACVIHRDLAARNCL
                                                   hTKT (L10717)
   L S M C Q D V C E G M E Y L E R N S F I H R D L A A R N C L
                                                   mTec (X5663)
544 VDRDLCVKVSDFGMTRYVLDDQYVSSVGTK
                                                  MKK2 aa
529 VNDQGVVKVSDFGLSRYVLDDEYTSSVGSK
                                                  hAtk (X58957)
490 VGENQVIKVSDFGMTRFVLDDQYTSSTGTK
                                                  hTKT (L10717)
   V N E A G V V K V S D F G M A R Y V L D D Q Y T S S S G A K
                                                  mTec (X5663)
574 FPVKWSAPEVFHYFKYSSKSDVWAFGILMW
                                                  MKK2 aa
559 FPVRWSPPEVLMYSKFSSKSDIWAFGVLMW
                                                  hAtk (X58957)
520 FPVKWASPEVFSFSRYSSKSDVWSFGVLMW
                                                  hTKT (L10717)
   F P V K W C P P E V F N Y S R F S S K S D V W S F G V L M W
                                                  mTec (X5663)
604 E V F S L G K Q P Y D L Y D N S Q V V L K V S Q G H R L Y R
                                                  MKK2 oo
hAtk (X58957)
                                                  hTKT (L10717)
                                                  mTec (X5663)
PHLASDTIYQIMYSCWHELPEKRPTFQQLL
619 PHLASEKVYTIMYSCWHEKADERPTFKILL
580 PRLASTHVYQIMNHCWKERPEDRPAFSRLL
483 PKLATKYLYEVMLRCWQERPEGRPSFEDLL
                                                  MKK2 oo
                                                  hAtk (X58957)
                                                  hTKT (L10717)
                                                  mTec (X5663)
664 SSIE PLREKDKH
                                                  MKK2 aa
649 SNIL DVMDEES
610 RQLAEIAES --- GL
513 RTIDELVECEETFGR
                                                  hAlk (X58957)
                                                  hTKT (L10717)
                                                  mTec (X5663)
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FIG.10C

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MSNICQRLWE-
                                                            MKK3 MPI
                                                                     aa
     MGCVQCKDKEA-T---KILTEERDGSLNQ-S
                                                            hFyn
     MGCVHCKEKIS-G---KGQGGSGTGTPAI-H
                                                            cYrk
     MGSNKSKPKDA-SQR-RRSLEPAENVHG-A
                                                            hSrc
     MGCIKSKENKS-PAI-KYRPENTPEPVS-T
                                                            hYes
     MGCVFCKKLEP-VATAKEDAGLEGDFRSYG
                                                            hFgr
     MGCIKSKGKDSLSDDGVDL-KTQPVRNTER
                                                            hLyn
     MGSMKSK---FLQVGGNTFSKTETSASPHC
                                                            hHck
     MGCGCSS----HPEDDWMENIDVCENCHY
                                                            hLck
     MGLLSSKRQVSEKGKGWSPVKLRTQDKAPP
                                                            mB1k
                                                            MKK3 MPI
                                                                     00
     SCYRYCTOPTPOHYPSFGVISIPN--YNNF
                                                            hFyn
    PPSOYDPDPT-QLSGAF--THIPD--FNNF
                                                            cYrk
     GGG AFPASQTPSKPASADGHRGPSAAFAPA
                                                            hSrc
     SVSHYGAEPITVSPCPSSSAKGTAVNFSSL
                                                            hYes
     AADHYGPDPTKARPAS-SFAHIPN--YSNF
                                                            hFgr
     T I Y V R D P T S N K Q Q R P V P E S Q L L P G Q R F Q T K
30
                                                            hLyn -
    PVYVPDPTSTIKPCPNSHNSNTPCIR--
28
                                                            hHck
    PIVPLDGKGTTLLTRNGSEVRD-PLVTYEGS
26
                                                            hLck
31
    PLPPLVVFNHLAPPSPNQ
                                                            mB1k
     YLPCLSTEADKSTVIENPGALCSPQSQRHG
                                                            MKK3 MPI aa
    HAA---GGQGLTVFGGVN--SSSHTGTLRT
54
                                                            hFyn
51
     HAA---AVSPPVPFSGPGFYPCNTLQAHSS
                                                            cYrk
58
                        KLIFGGIFNSSDTVTSPQRAG
                                                            hSrc
58
    SMTPFGGSSGVTP|FGG|ASSSFSVVPSSYPA
                                                            hYes
57
                                                            hFgr
60
        E E - - - - - - - Q G -
                                                            hLyn
54
     EAG S
                                                            hHck
55
    NPPA-----------
    DPDE-----FF
                                                            mBik
   H - - - - - YF V A LFD YQAR TAED L SFR AGDK
R G G T G V T L F V A L Y D Y E A R T E D D L S F H K G E K
I T G G G V T L F I A L Y D Y E A R T E D D L S F Q K G E K
P L A G G V T I F V A L Y D Y E S R T E T D L S F K K G E R
G L T G G V T I F V A L Y D Y E A R T E D D L T F T K G E K
V S G I G V T L F I A L Y D Y E A R T E D D L T F T K G E K
- - - - - - D I V V A L Y P Y D G I H P D D L S F K K G E K
- - - - - - N L V I A L H S Y E P S H D G D L G F E K G E Q
- - - - - - R F V V A L F D Y A A V N D R D L Q V L K G E K
                                                           MKK3
                                                                MPI aa
                                                           hFyn
                                                           cYrk
                                                           hSrc
                                                           hYes
74
                                                           hfgr
66
                                                           hLyn
60
                                                           hHck
64
                                                           hLck
55
                                                           mB1k
```

FIG.11A

Title: NOVEL MEGAKARYOCYTIC PROTEIN TYROSINE KINAGES

Inventor(s): Axel ULLRICH et al. Appl. No.: 08/426,509

```
LQVLDTLHEGWWFARHLEKRRDGSSQQLQG
                                                                    MKK3 MPI
                                                                               00
    FQTLNSSEGDWWEARSLITTGETG-
                                                                    hFyn
    FHIINNTEGDWWEARSLSSGATG
108
                                                                     cYrk
     LQIVNNTEGDWWLAHSLSTGQTG
                                                                     hSrc
     FIQ I I I N N T E G D W W E A R S I A T G K N G
                                                                     hYes
118
                                                                     hFgr
104
                                  RSLSSGKTG
         VLEEH-GEWWKAKSLLTKKEG
                                                                     hLyn
         VILIE E S - GEWWKIAR S LIAITRKEG
84
                                                                     hHck
88
     LIRILE QS-GEWWKAQSLITT GQEG
                                                                     hLck
     L QVLR ST-GDWWLARSLV
                                                                     mBlk
     YIPSNYVAEDRSLQAEPWFFGAIGRSDAEK
                                                                     MKK3 MPI
                                                                               OO.
     Y I P S N Y V A P V D S I Q A E E W Y F G K L G R K D A E R
132
                                                                     hFyn
           S N Y V A P V D S I I Q A E E W Y F G K I G R K D A E R
131
                                                                     cYrk
       I P S N Y V A P S D S I Q A E E W Y F G K I T R R E S E R
134
                                                                     hSrc
         P S N Y V A P A D S I I Q A E E W Y F G K M G R K D A E R
                                                                     hYes
     C I P S N Y V A P V D S I Q A E E W Y F G K I G R K D A E R
                                                                     hFgr
     F I P S N Y V A K L N T [ ] E T | E E W F F | K D | I | T | R K D A E R
112
                                                                     hLyn
    YIPSNYVARVDSLETEEWFFKGIISRKDAER
                                                                     hHc k
110 FLPENFVAKANSLEPEPWFFKNLSRKDAER
                                                                     hLck
     YVPSNFVAPVETLEVEKWFFRTISRKDAER
101
                                                                     mB1k
     Q L L | Y S E N K T G S F L I R E S E | S Q K G E F | S L S V | L | D |
                                                                     MKK3 MPI
                                                                               00
162 QLLSFGNPRGTFLIRESETTKGAYSLS[[RD]
                                                                     hFyn
     Q L L C H G N C R G T F L I R E S E
                                                                     cYrk
164 LILLNAENPRGITFLVRESE
                                                                     hSrc
     LLLNPGNQRGIIFLVRESET
171
                                                                     hYes
    Q L L S P G N P Q G A F L T R E S E T T K G A Y S L S I R D
157
                                                                     hLyn
     QLLAPGNSAGAFLI
                                  RESETLKGSFSLSVRD
142
                                                                     hHc k
     Q L L A P G N M L G S F M I R D S E T T K G S Y S L S V R D
                                                                     hHck
140 QLLAPGNTHGSFLIRESESTAGSFSLSVRD
131 QLLAPMNKAGSFLIRESESNKGAFSLSVKD
                                                                     hLck
                                                                     mB1k
159 ----GAVVKHYRIKRLDEGGFFLTRRRIF
192 WDDMKGDHVKHYKIRKLDNGGYYITTRAQF
191 WDEAKGDHVKHYKIRKLDSGGYYITTRAQF
194 FDNAKGLNVKHYKIRKLDSGGFYITSRTQF
201 WDEIRGDNVKHYKIRKLDNGGYYITTRAQF
                                                                     MKK3 MPI
                                                                               00
                                                                     hFyn
                                                                     cYrk
                                                                     hSrc
                                                                     hYes
187 W D Q T R G D H V K H Y K I R K L D M G G Y Y I T T R V Q F 172 F D P V H G D V I K H Y K I R S L D N G G Y Y I S P R I T F 166 Y D P R Q G D T V K H Y K I R T L D N G G F Y I S P R I T F 170 F D Q N Q G E V V K H Y K I R N L D N G G F Y I S P R I T F 161 I T T - Q G E V V K H Y K I R S L D N G G Y Y I S P R I T F
                                                                     hFgr
                                                                     hLyn
                                                                     hHck
                                                                     hLck
                                                                     mBlk
```

```
STLNEFVSHYTKTSDGLCVKLGKPCLKIQV
 184
                                                      MKK3 MPI
                                                              QQ
 222 ETLOQLVQHYSERAAGLCCRLVVPCHKGM-
                                                      hFyn
    DITIQQL V Q H Y I E R A A G L C C R L A V P C P K G T -
                                                      cYrk
 224 NSLOQLVAYYSKHADGLCHRLTTVCPTSK-
                                                      hSrc
    DITLOKLVKHYTEHADGLCHKLTIVCPTVK -
                                                      hYes
 217
    NSVQELVQHYMEVNDGLCNLLIAPCTIMK -
                                                      hFgr
    PCISDMIKHYQKQADGLCRRLEKACISPK-
 202
                                                      hLyn
 196 SILQELVDHYKKGNDGLCQKLSVPCMSSK-
                                                      hHck
    POLHEL VRHYINASDGLCIRUS RPCQTQK-
 200
                                                      hLck
    PTLQALVQHYSKKGDGLCQKLTILPCVNLA-
                                                      mBlk
    PAPFOLLSYKTVOQWEIDRNSLOLLKRLGSG
                                                      MKK3 MPI
                                                             00
    PRLTDLSVKITKDVWEIPRESLOLIKRLGNG
 251
                                                      hFyn
    PKLADLSVKITKDVWEIPRESLIQILLQKLGNG
 250
                                                      cYrk
 253
    POTOGILA - - KDAWEIPRESLIRLEVKLGOG
                                                      hSrc
    POTOGILA -- KDAWEIPRESLIRILEVKLGOG
 260
                                                      hYes
 246
    POTLGLA---KDAWEISRSSITLERRLGTG
                                                      hFgr
    PQ----KPWDKDAWEIPRESIKLVKRLGAG
 231
                                                      hLyn
 225
    PQ----KPWEKDAWEIPRESLKLEKKLGAG
                                                      hHc k
 229
    PQ----KPWWEDEWEVPRETLKLVERLGAG
                                                      hLck
    PK----NLWAQDEWEIPRQSLKLVRKLGSG
 219
                                                      mBlk
    Q F G E V W E G L W N N T T P V A V K T L K P G S M D P N D
                                                      MKK3 MPI
                                                             00
 281
    QFGEVWMGTWNGNIKVAIIKTLKPGTMSPES
                                                      hFyn
280
    QFGEVWMGTWNGTT<u>K</u>VA<u>V</u>KTLKPGTMSPEA
                                                      cYrk
280
    CFGEVWMGTWNGTTRVAIKTLKPGTMSPEA
                                                      hSrc
287 CFGEVWMGTWNGTTKVALIKTLKPGTMMPEA
                                                     hYES
    C F G D V W L G T W N G S T K V A V K T L K P G T M S P K A
273
                                                     hFgr
    QFGEVWMGYYNNSTKVAVKTLKPGTMSVQA
                                                     hLyn
    Q F G E V W MATYNKHTK V A V K TMK P G S M S V E A
251
                                                     hHck
255 OFGEVWMGYYNGHTKVAVKSLKOGSMSPDA
                                                     hLck
245 QFGEVWMGYYKNNMKVATIKTLKEGTMSPEA
                                                     mB1k
274 F LREAQIMKNLRHPKLIQLYAVCILEDPIY
274 | LREAQIMKNL RHPK LIJULYAVU I LEUPIT

311 | FLEEAQIMKKLKHDKLVQLYAVVS - EEPIY

310 | FLQEAQVMKKLRHEKLVQLYAVVS - EEPIY

317 | FLQEAQIMKKLRHEKLVQLYAVVS - EEPIY

303 | FLEEAQVMKLLRHDKLVPLYAVVS - EEPIY

287 | FLEEANLMKTLQHDKLVRLYAVVTREEPIY

281 | FLAEANVMKTLQHDKLVKLHAVVTKE-PIY

285 | FLAEANLMKQLQHQRLVRLYAVVTRE-PIY

275 | FLGEANVMKTLQHERLVRLYAVVTRE-PIY
                                                     MKK3 MPI
                                                             00
                                                     hFyn
                                                     cYrk
                                                     hSrc
                                                     hYes
                                                     hFgr
                                                     hLyn
                                                     hHck
                                                     hLck
                                                     mBlk
```

FIG. 11C

21/26 304 TELMRHGSTOFYTONDTGSKI HOTDOVO		
340 IVTEYMNKGSLLDFIKDGEGRAFKIPNEVO	MKK3 MPI hFyn	00
339 IVTEFMSQGSLLDFLKDGDGRYLKLPQLVD 339 IVTEYMSKGSLLDFLKGETGKYLRLPQLVD	cYrk hSrc	
346 I V T E F M S K G S L L D F L K E G D G K Y L K L P Q L V D	hYes	
332 IVTEFMCHGSLLDFLKNPEGQDLRLPQLVD 317 IITEYMAKGSLLDFLKSDEGGKVLLPKLTD	-	
310 I I TEFMAKGSLLDFLKSDEGSKQPLPKLID	hLyn hHck	
314 ITITEY MENIGS LIVIDEL KITP SIGIIK LITTN KILILIDI	hLck	
304 IVTEYMARGCLLDFLKTDEGSRLSLPRLID	mBlk	
334 MAAQVASGMAYLESRNYIHRDLAARNVLVG	MKK3 MP[00
370 MAAQVAAGMAYIERMNUIHRDLRSANILVG 369 MAAQIAAGMAYIERMNYIHRDLRAANILVG	hFyn	
369 MAAQIAAGMAYIERMNYIHRDLRAANILVG 369 MAAQIASGMAYVERMNYVHRDLRAANILVG	cYrk hSrc	
376 MAAQIADGMAYIERMNYIHRDLRAANILVG	hYes	
362 MAAQIVIAEGMAYIMERMNYTHRDIRAANII VOL	hFgr	
347 F S A Q I A E G M A Y I E R K N Y I H R D L R A A N V L V S 340 F S A Q I A E G M A F I E Q R N Y I H R D L R A A N I L V S	hL yn	
344 MAAQIAEGMAFIIEERNYIHRDLRAANTIVS	hHck hLck,	
334 MSAQVAEGMAYIERMNSIHRDLRAANILVS	mBlk	
364 EHNIYKVADFGLARVFKVDNEDIYESRHEI	MKK3 MPI	00
400 NGLICKIADFGLARLI EDNEYTAROGA 399 DNLVCKIADFGLARLI EDNEYTAROGA	hFyn	
399 DNLVCKIADFGLARLIEDNEYTARQGA 399 ENLVCKVADFGLARLIEDNEYTARQGA	cYrk hSrc	
406 ENLYCKIADFGLARLIIEDNEYTAROGAL	hYes	
392 ERLACKIADFGLARLI KDDEYNPCOGS 377 ESLMCKIADFGLARVI FDNEYTARECA	hFgr	
377 ESLMCKIADFGLARVI EDNEYTAREGA 370 ASLVCKIADFGLARVI EDNEYTAREGA	hLyn hHck	
3/4 DILISICKIADFGLARLIIEDNEYTARIFIGAL	hLck	
364 ETLCCKIADFGLARTII DSEYTAGEGA	mBlk	
394 KLPVKWTAPEALRSNKFSIKSDVWSFCILL	MKK3 MPI	00
427 KFPIKWTAPEAALLYGRFTIKSDVWSFGILL	hFyn	
426 KFPIKWTAPEAALFGKFTIKSDVWSFGILL 426 KFPIKWTAPEAALYGRFTIKSDVWSFGILL	cYrk hSrc	
433 KFPIKWTAPEAAL Y GRFTIKSDVWSFGILTO	hYes	
419 KFPIKWTAPEAALFGRFTIKSDVWSFGILTI	hFgr	
404 KFPIKWTAPEAINFGCFTIKSDVWSFGILL 397 KFPIKWTAPEAINFGSFTIKSDVWSFGILL	hLyn hHck	
401 KFPIKWTAPEAINYGTFTIKSDVWSFGILI	hLck	
390 KFPIKWTAPEAIHFGVFTIKADVWSFGVLL	mBlk	

FIG.11D

```
YEI ITYGK MPYSGMTG A QVI QML A QNYRLP
                                                     MKK3 MPI
                                                             00
457
                                                     hFyn
456
                       G M N N R E V L E Q V E R G Y R M Q
                                                     cYrk
456
    T E L|T|T K G R V P Y P G M|V |N R E V L|D|Q V E R G Y R M P|
                                                      hSrc
    TEL<u>V</u>TKGRVPYPGM|V|NREVLEQVERGYRMP|
                                                      hYes
       LITKGR[]PYPGMNKREVLEQVEQQGYHMP
                                                      hFgr
    YEIV TYGK IP Y P GRT NAD VM T A L S Q G Y R M P
                                                      hLyn
    MEIVTYGRIPYPGMSNPEVIRALERGYRMP
                                                      hHck
   TEIV THG RUPYPGMTNPEVION LERGYRMV
                                                     hLck
    MVIVTYGRVPYPGMSNPEVIRSLEHGYRMP
                                                     mBlk
   OPSNCPQOFYN-IMLECWNAEPKERPTFET
                                                     MKK3 MPI
    CPQDCPISLH-ELMIHCWKKDPEERPTFEY
                                                      hFyn
    C PG GC PPS LH - DVMVQ C W KREPEERPTFEY
                                                      cYrk
    CPPECPESLH-DLMCQCWRKEPEERPTFEY
                                                      hSrc
    CPQGCPESLH-ELMNLCWKKDPDERPTFEY
                                                      hYes
    CPPGCPASLY-EAMEQTWRLDPEERPTFEY
                                                     hFgr
    R V E N C P D E L Y - D I M K M C W K E K A E E R P T F D Y
                                                     hLyn
    RPENCPEELY-NIMMRCWKNRPEERPIFEY
                                                     hHc k
    RPDNCPEELY-QLMRLCWKERPEDRPTFDY
                                                     hLck
   C P E T C P P E L Y N D I I T E C W R G R P E E R P T F E F
                                                     mB1k
                                                     MKK3 MPI
                                                             00
                                                     hFyn
    |LQSFLEDYFTATEPQYQPG|D|N|---Q
                                                      cYrk
515 LQAFLEDYFTSTEPQYQPGEN---L
522 IQSFLEDYFTATEPQYQPGEN---L
508 LQSFLEDYFTSAEPQYQPGDQ---T
493 LQSVLDDFYTATEGQYQQ--Q---P
486 IQSVLDDFYTATEGQYQQ--Q---P
490 LRSVLEDFFTATEGQYQP--Q----P
                                                      hSrc
                                                     hYes
                                                     hFgr
                                                     hLyn
                                                     hHck
                                                     hLck
    LOSVLEDFYTATEGOYEL
480
                                                     mB1k
```

FIG.11E

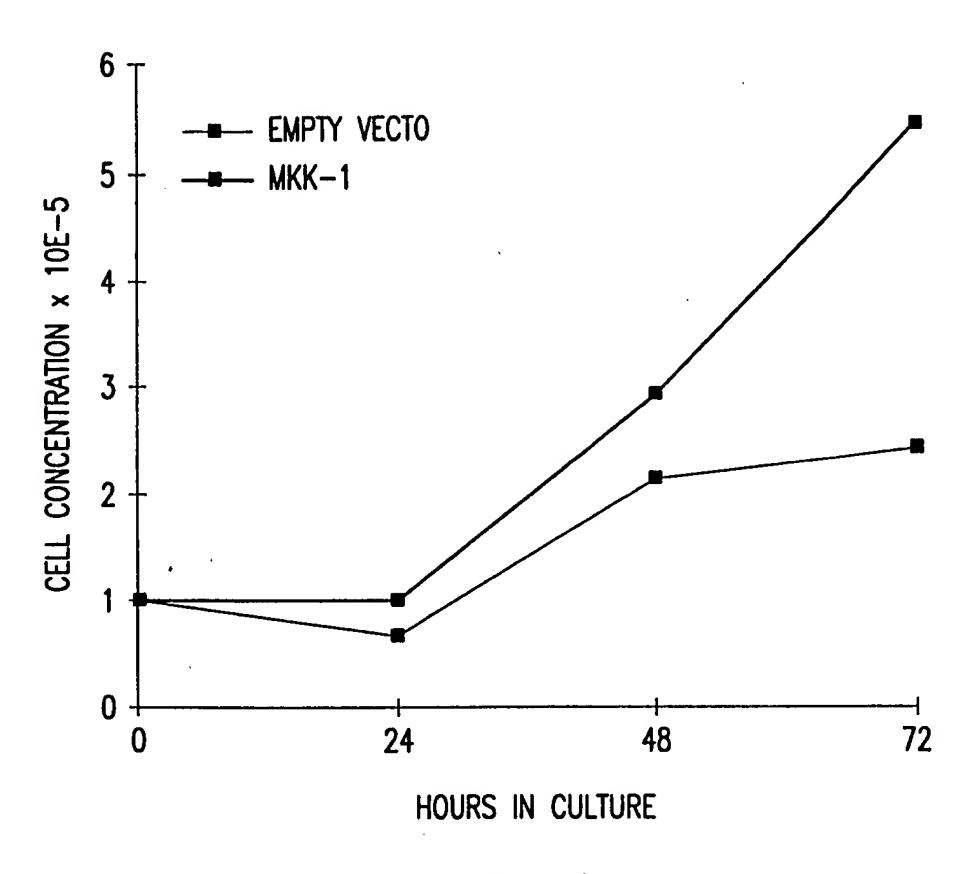


FIG. 12

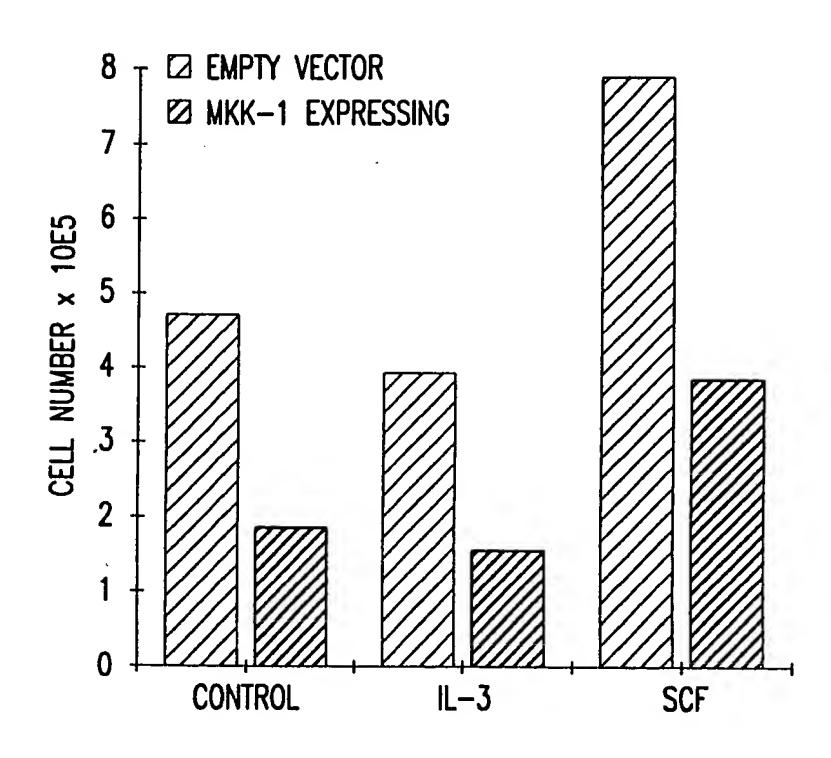
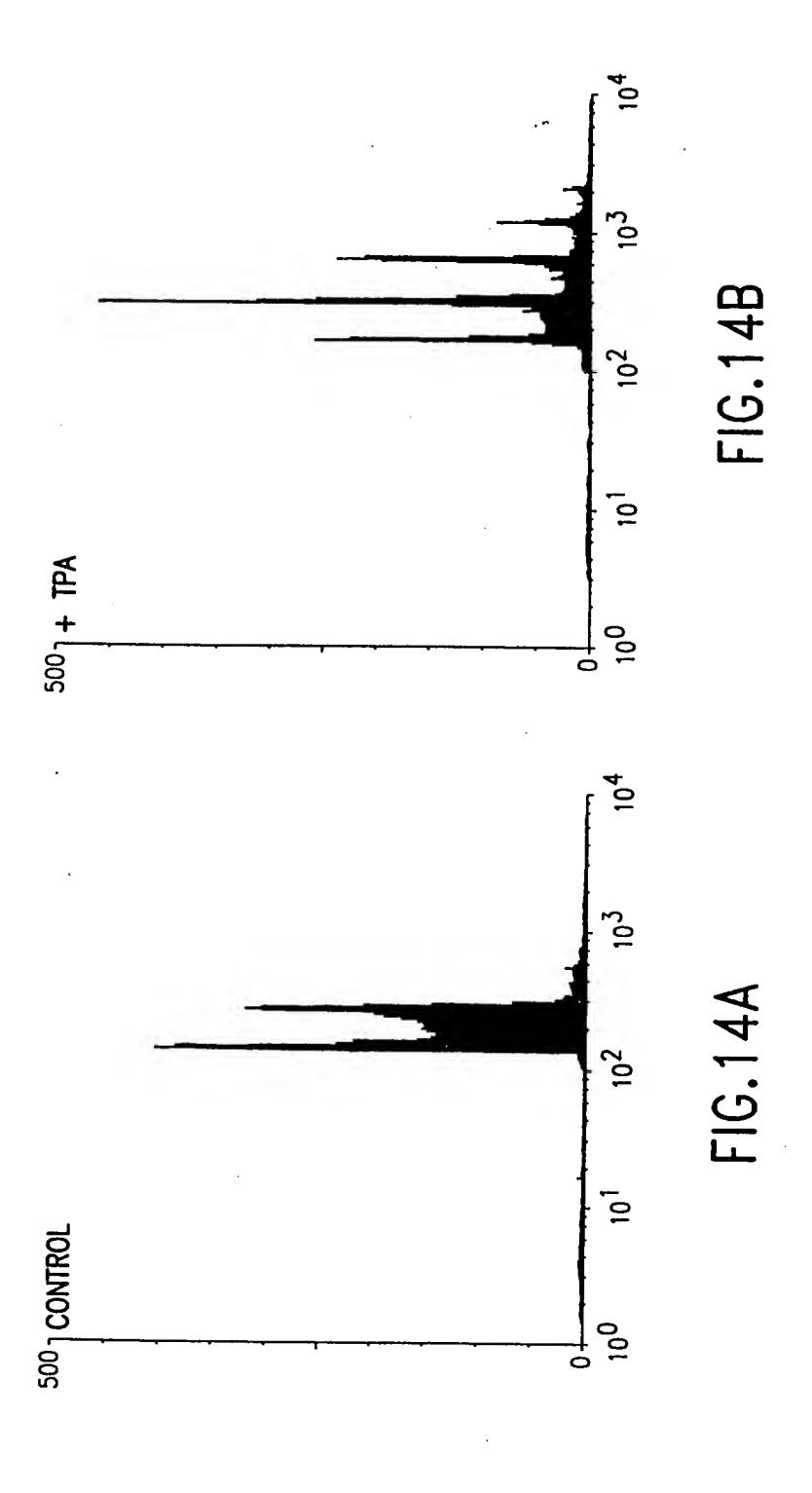


FIG.13



Title: NOVEL
MEGAKARYOCYTIC PROTEIN
TYROSINE KINASES
Inventor(s): Axel ULLRICH et al.
Appl. No.: 08/426,509

